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Health and Environmental Effects Profile for EPTC

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR EPTC

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OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT
OFFICE OF RESEARCH AND DEVELOPMENT
U.S. ENVIRONMENTAL PROTECTION AGENCY
CINCINNATI, OH 45268

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16. ABSTRACT

The Health and Environmental Effects Profile for EPTC was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. EPTC has been determined to be a systemic toxicant. An Acceptable Daily Intake (ADI), defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect, for EPTC is 5×10^{-2} (mg/kg bw/day) for oral exposure.

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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents.The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched."

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include, Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor or q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA docket.

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Scientists from the following U.S. EPA offices provided review comments for this document series:

Environmental Criteria and Assessment Office, Cincinnati, OH
Carcinogen Assessment Group
Exposure Assessment Group
Reproductive Effects Assessment Group

Editorial review for the document series was provided by:
Judith Olsen and Erma Durden
Environmental Criteria and Assessment Office, Cincinnati, OH

Technical support services for this document series were provided by:
Bette Zwayer, Pat Daunt, Karen Mann, and Jacky Bohanon
Environmental Criteria and Assessment Office, Cincinnati, OH.

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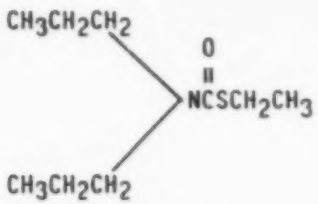
LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
BCF	Bioconcentration factor
bw	Body weight
DNA	Deoxyribonucleic acid
GC	Gas chromatography
i.p.	Intraperitoneal
K_{oc}	Soil adsorption coefficient
LC_{50}	Concentration lethal to 50% of the recipients (and all other subscripted dosage levels)
LD_{50}	Dose lethal to 50% of the recipients
NOAEL	No-observed-adverse-effect-level
ppb	Parts per billion
ppm	Parts per million
ppt	Parts per trillion
RNA	Ribonucleic acid
STORET	Water Quality Control Information System (Storage and Retrieval)
TLC	Thin layer chromatography

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

EPTC is the common name for S-ethyl dipropylcarbamothioate. This compound is also known as S-ethyl dipropylthiocarbamate, carbamothioic acid, dipropyl-, S-ethyl ester and carbamic acid, dipropylthio-, S-ethyl ester (BCPC, 1977; U.S. EPA, 1983a). This herbicide was introduced under the trade name of Eptam or Eradican and code number "R-1608" by Stauffer Chemical Company in 1954. The structure of EPTC is given below:



Molecular formula: $C_9H_{19}NOS$

Molecular weight: 189.3

The Chemical Abstracts Service (CAS) Registry Number for this compound is 759-94-4.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

EPTC is a liquid with a light yellow color and aromatic or amine odor (BCPC, 1977; Sanborn et al., 1977). Some of the physical properties are given below:

Boiling point:	127°C at 20 mm of Hg (Sanborn et al., 1977)
Density at 30°C:	0.9546 g/mℓ (BCPC, 1977)
Solubility in water:	375 ppm at 24°C (Freed et al., 1967)
Vapor pressure:	0.1 mm of Hg at 24°C (Sanborn et al., 1977)
Estimated bioconcentration factor:	12-22 (Kenaga, 1980)

1.3. PRODUCTION DATA

EPTC, a thiocarbamate herbicide, is produced by the Stauffer Chemical Company by reacting ethyl chlorothiolformate with di-n-propylamine (Ayers et al., 1976). Recent production data for the United States are unavailable, although an earlier study estimated that in 1971 production was 5 million pounds/year (Lawless et al., 1972).

1.4. USE DATA

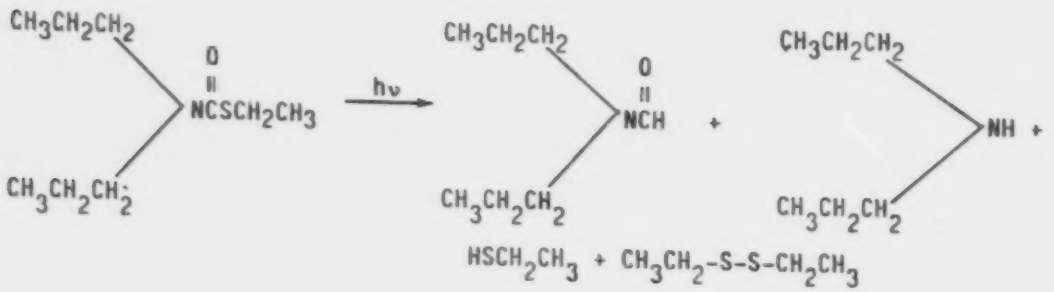
EPTC is used as a pre- and postemergence herbicide on a wide variety of agricultural commodities.

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

There are only limited data on the fate and transport of EPTC in air. The likely routes of entry for EPTC into the atmosphere are through volatilization from soil and water. In a laboratory study, Koren et al. (1969) determined the loss due to volatilization of EPTC applied as an aqueous solution to five soil types. After 1 hour at 40°C under slowly moving air, 5.3-18.1% of the applied EPTC was lost from different kinds of soils. Volatilization was related to the water content of the original soil and the length of time for drying rather than the organic content of the soil. Similar results were reported by Cliath et al. (1980) in a field study in which EPTC was applied to an alfalfa field in the irrigation water at a level of 3.04 kg/ha. After 52 hours, atmospheric measurements of air samples collected using a pesticide collection mast composed of six polyurethane foam plug collectors indicated that 73.6% of the applied herbicide was lost to the air by volatilization. It was estimated using Parshall flumes that 0.86 kg of EPTC were lost from the water and 1.38 kg were lost from wet soil.

The fate of EPTC in the atmosphere will depend upon its reactions with O_3, NO_x and free radicals (e.g., RO•, O• and RO_2•) and its ability to undergo photolysis. Although there is no information on the reaction of EPTC with the atmospheric reactants, there are limited data on the photolysis of EPTC. DeMarco and Hayes (1979) exposed a hexane solution of EPTC to light from a medium pressure mercury lamp. An initial decomposition rate of 0.02 mol/ℓ/min was determined by removing samples from the photolysis

chamber at various times following 10-minute equilibrations and determining by GC the herbicide disappearance. The products of the reaction were identified as follows:



Since this study of DeMarco and Hayes (1979) was conducted with ultraviolet light in the liquid phase, it is difficult to extrapolate the results to predict the photochemical reactivity of EPTC in the atmosphere.

EPTC can enter the aquatic media through runoff and leaching from soil. The fate of EPTC in the aquatic media has been studied to a limited extent. Cliath et al. (1980) observed extensive volatilization of EPTC when applied in irrigation water. Volatilization occurred from both water and wet soil. In 52 hours of observation, 73.6% of the applied EPTC volatilized and 7% was removed by runoff water. Other likely mechanisms for removal of EPTC from water include photochemical reaction, free radical reaction, hydrolytic reaction and biodegradation. The study by DeMarco and Hayes (1979) indicates that EPTC has the potential for photolysis, and studies in soil indicate that biodegradation may be a significant process for removal of EPTC from water; however, there are no specific studies regarding these processes in water.

The fate and transport of EPTC has been studied most extensively in soil. The major process for removal of EPTC from wet soil is volatilization. Soil conditions that affect volatilization were examined by Gray and

Weierich (1968a). After spray application (equivalent to 3.2 pounds/acre) to most soils, 24, 78 and 86% of the herbicide was volatilized by 0.5, 2 and 6 hours after treatment. There was little effect of temperature on compound loss between 32 and 100°F, however, moisture content dramatically affected compound loss. At 17% moisture, 10% of the compound was lost in the first hour and 60% lost by 24 hours, while in dry soil, only 15% was lost by 144 hours. It is expected that soil type would also affect the rate of volatilization as shown for other thiocarbamate herbicides (Gray and Weierich, 1968a). Data for EPTC were not presented.

Leaching and biodegradation of EPTC are also important mechanisms for removal of EPTC from soil. Using soil columns, Harris (1967), Buzio and Burt (1980), Koren et al. (1969) and Gray and Weierich (1968b) studied the effects of soil types and other environmental conditions on the leaching rate of EPTC. In a comparison on a scale of 1-6 (1 = no movement, 6 = maximum movement) of the mobility of 28 herbicides in soil, EPTC was observed to have a mobility of 2.6 (Harris, 1967). Gray and Weierich (1968b) used five different soil types with clay contents ranging from 4.6-33.2% and organic matter ranging from 4.6-34.6% for comparison with the rate of leaching of EPTC. The depth of leaching was shown to decrease as both the clay and organic matter increased, with no movement observed in Egbert peat that contained 17.6% clay and 34.6% organic matter. Koren et al. (1969), using five soils with clay contents of 2-28.8% and organic contents of 0.52-51.8%, observed increased rates of leaching with decreased organic matter, but observed no effect of clay content on the movement of this herbicide. Although downward movement of EPTC was observed as water percolated through the soil, upward movement occurred as the column was allowed to dry over a 6-day period. These competing actions may maintain higher effective levels

of EPTC near the soil surface. The relatively low K_{oc} values (Kenaga, 1980) of 240 and 170 as determined experimentally and theoretically, respectively, would support the moderate mobility observed for EPTC in soil columns.

Biodegradation of EPTC was initially indicated in an early study by Sheets (1959) where a decrease in the rate of inactivation of the phytotoxicity of EPTC was observed in sterile soil as compared with soil that had not been autoclaved. Similar results were demonstrated by MacRae and Alexander (1965) and Koren et al. (1968), who also observed more rapid degradation of EPTC in nonsterile soil. The loss of EPTC in the sterile soil was shown to be more rapid if the soil had been treated previously with EPTC (Obrigawitch et al., 1982). It was also observed that the rate of EPTC breakdown was more rapid with a soil moisture content of 3-16% and at temperatures between 15 and 25°C than at a lower moisture content of 1.6% and a temperature of 5°C. At the lower temperature the half-life of EPTC was 40 days, while the half-life was 12-13 days at the higher temperature. Field studies confirmed these laboratory findings with half-lives of 9 and 18 days, respectively, for fields previously tested with EPTC and those with no prior treatment that had soil moisture levels of 5.5-21% during the study. Addition of manure or sewage sludge to the soil did not appreciably alter the degradation of EPTC (Kaufman and Doyle, 1977; Doyle et al., 1978).

The fate of EPTC in soil also could be governed by non-biological reactions such as chemical and hydrolytic reactions. Smith and Fitzpatrick (1970) observed a 50% loss of EPTC in 1 hour with 29 N H_2SO_4 at 75°C and negligible hydrolysis in 1 hour with 10 N NaOH at 79°C. This suggests that it is unlikely that hydrolysis will be a major removal process under environmental conditions. Photolysis of EPTC has been shown to occur in hexane

solution under a mercury lamp. DeMarco and Hayes (1979), however, reported that sunlight exposure of EPTC adsorbed onto silica gel-coated TLC plates for 16 hours did not result in the photodegradation of EPTC. The importance of other chemical reactions in the disappearance of EPTC from soil has not been investigated.

In field studies, Smith and Hayden (1982) incorporated EPTC into the top 10 cm of test plots at an equivalent application rate of 4 kg/ha. In three regions of Saskatchewan three test plots were selected with the soils in these regions consisting of heavy clay, clay loam and sandy loam. Chemical analysis of the soils 22 weeks after application revealed that EPTC residue remained at 7% in the clay loam and was undetectable (<2% of the amount applied) in the other soils. The authors concluded that EPTC would not persist from one growing season to another.

An estimated BCF of 12-22 (Kenaga, 1980) indicates a very low bioconcentration potential for EPTC.

3. EXPOSURE

STORET contains monitoring data on EPTC in water and sediments for a limited number of samples. There are 139 observations for EPTC in sediments and 180 observations for water collected between 1974 and 1976 in the Pacific Northwest. None of the sediment or water samples showed detectable levels of EPTC at a detection limit of 15 µg/kg for sediments and between 15 µg/ℓ and 20 µg/ℓ for water samples. Spalding et al. (1980) analyzed EPTC in the ground of an agricultural region of Nebraska. Samples were collected from 14 sites where groundwater NO_3-N was >10.0 mg/ℓ, indicating percolation into the groundwater from farm land. The EPTC concentration in these samples was <0.01 µg/ℓ. Konasewich et al. (1978) detected EPTC in Lake Erie, however, levels of EPTC were not reported. Monitoring data for EPTC in ambient air and in edible foods could not be found.

4. PHARMACOKINETICS

4.1. ABSORPTION

Data relating specifically to the absorption of EPTC were not found in the available literature; however, some information was obtained from metabolism studies. Ong and Fang (1970) reported peak elimination as $^{14}CO_2$ within 1-2 hours after oral dosing of rats with 2.3-78.8 mg ethyl-1-^{14}C-EPTC/kg. Mice receiving an oral dose of 100 mg ethyl-1-^{14}CEPTC/kg expired 35% of the radiolabel as $^{14}CO_2$ within 12 hours and 25% of the administered radioactivity in the urine within 48 hours (Casida et al., 1975). These studies indicate that EPTC is rapidly absorbed from the gastrointestinal tracts of rats and mice.

4.2. DISTRIBUTION

Hubbell and Casida (1977) measured tissue radioactivity 48 hours after oral administration of ^{14}C=O-EPTC to rats at levels of 13.5 or 132.5 mg/kg. At the low dose, 3.3% of the administered radioactivity was retained in the body and levels of radioactivity equivalent to 1340 ppb of the administered compound in blood, 1000 ppb in kidney, 2980 ppb in liver and a range of 200-960 ppb in other tissues (brain, fat, heart, lung, muscle, spleen and testes). At the high dose, 1.4% of the administered radioactivity was retained with 14,740 ppb in blood, 5500 ppb in kidney, 7810 ppb in liver and a range of 890-4870 ppb in the other tissues. The concentrations of radioactivity reflect the distribution of EPTC and/or metabolites and do not reflect the tissue distribution of EPTC per se.

4.3. METABOLISM

The metabolism of EPTC has been studied in mice and rats in both *in vivo* and *in vitro* systems.

Ong and Fang (1970) reported that metabolism of ethyl-1-^{14}C-EPTC to $^{14}CO_2$ was essentially complete (85% of the administered radiolabel) within 15 hours of oral administration of ~2.3 mg ^{14}C-EPTC/kg to female rats. At least six radiolabeled metabolites were found in the 96-hour urine, accounting for 8.4% of the administered dose. As the dose was increased, proportionately less radioactivity was detected as $^{14}CO_2$ and it appeared at later times and more radioactivity was excreted as urinary metabolites (at ~385 mg/kg, 35.6% of the radioactivity was in the urine and 38.2% was detected as CO_2). No dose-related differences in $^{14}CO_2$ liberation and percent radioactivity in urinary products were noted by Hubbell and Casida (1977) 48 hours after dosing rats with up to 1/3 (132.5 mg/kg) of the maximum dose used by Ong and Fang (1970).

Casida et al. (1974, 1975) studied the sulfoxidation of EPTC by mice in vivo and by mouse liver microsomes in vitro. ^{14}C=O labeled preparations of EPTC, EPTC sulfoxide or EPTC sulfone were administered orally at a level of 100 mg/kg to male mice. Within 12 hours, $^{14}CO_2$ liberation was complete and the percent recoveries of administered doses in expired air were 35, 41 and 6% for the respective compounds. Urinary metabolites (at least seven) accounted for 25, 57 and 87% of the administered radioactivity of each respective compound. The major metabolite of all three compounds was ethylmethyl sulfone. The sulfoxide, a proposed transient metabolic intermediate of EPTC in mammalian systems, was detected in the livers of mice within 10 minutes following i.p. injection of 1 mmole EPTC/kg, but was no longer detected at 60 minutes. Sulfone was not detected in the livers, but it was not expected to persist because it is hydrolytically unstable (Casida et al., 1975).

When ^{14}C-EPTC was incubated with mouse liver microsomes and NADPH, ~44% was metabolized and EPTC sulfoxide (14% of initial radioactivity), but not EPTC sulfone, was formed. N-depropyl EPTC (1%), three organosoluble metabolites (2%) and water soluble metabolites (21%) were also formed. The extent of EPTC metabolism increased to 63-68% when the soluble enzymes and glutathione (GSH) were added to the incubation system, a volatile "mercaptan" was liberated, and the sulfoxide recovery decreased. These findings suggested that reaction of GSH with EPTC sulfoxide results in a cleavage of the carbamoyl bond by GSH attack at the carbonyl group (perhaps catalyzed by GSH-S-transferase) liberating either the mercaptan or sulfonic acid (Casida et al., 1974). In vivo, this fragment may have been metabolized by two different pathways, one in which CO_2 was formed, the other in which methylation and oxidation resulted in the formation of ethyl methyl sulfone (Casida et al., 1975).

Hubbell and Casida (1977) further characterized the metabolism of EPTC by rats based upon identification of the 48-hour urinary metabolites of ^{14}C=O labeled preparations of EPTC (13.5 and 132.5 mg/kg) or EPTC sulfoxide (13 mg/kg) administered orally to rats, or S-(N,N-dipropyl carbamoyl-GSH (0.49 mg/kg) or S-(N,N-dipropylcarbamoyl)-cysteine (0.13 mg/kg) administered intraperitoneally to rats. The metabolites from all compounds were essentially the same qualitatively and quantitatively. The metabolites for ^{14}C=O-EPTC included, as percent of urinary radiocarbon, 15.2% as the cysteine conjugate, 50.7% as the mercapturic acid derivative, 3.4% as mercaptoacetic acid derivative and ~30% as at least 10 other metabolites. In addition, the mercapturic acid was detected by GC as 18% on a molar basis of the administered compound in the urine 24 hours after i.p. administration of

unlabeled EPTC at 1.0 mmole/kg to rats, and the GSH conjugate was detected by TLC in rat livers 30 and 135 minutes after i.p. injection of 1.0 mmole/kg EPTC sulfone.

The major pathway suggested by these results is: EPTC → EPTC sulfoxide → GSH-conjugate → cysteine conjugate → mercapturic acid derivative and mercaptoacetic acid derivative (Hubbell and Casida, 1977).

In vitro metabolism of EPTC by mouse liver microsomes involved mono- and dioxygenation at the sulfur and hydroxylation at each alkyl carbon (Chen and Casida, 1978). ^{14}C=O or [ethyl-^{14}C] labeled preparations of EPTC (0.68 μmol), EPTC sulfoxide (0.36 μmol) or EPTC sulfone (0.45 μmol) were incubated with the mouse liver microsomal system (1.5 mℓ) in the presence of NADPH. The major compound present after incubation of ^{14}C=O-EPTC and ^{14}C=O-EPTC sulfoxide was EPTC sulfoxide (50.9% from EPTC, 87.7% from the sulfoxide). EPTC sulfone was the major compound identified after incubation of ^{14}C=O-EPTC sulfone and was a metabolite of ^{14}C=O-EPTC sulfoxide (1.6%), but was not detected as a metabolite of ^{14}C=O-EPTC, unless precarbamoylated microsomes were used. Other metabolites of ^{14}C=O that retained the ester bond were N-depropyl EPTC (2.1%), β-hydroxypropyl EPTC (1.9%), γ-hydroxypropyl EPTC (1.3%) and β-hydroxyethyl EPTC (0.4%). Cleavage products included carbonyl sulfide (COS, 4.9%), CO_2 (1.3%) and some unknown compounds. No COS or CO_2 were formed from the sulfoxide or the sulfone. Metabolism of ethyl-^{14}C-EPTC resulted in 25.3% EPTC sulfoxide, 2.1% N-depropyl EPTC, 3.2% β-hydroxypropyl EPTC, 2.1% γ-hydroxypropyl EPTC and additional unknowns. The proposed pathway based on these studies involves oxidation at the sulfur to yield EPTC sulfoxide, which is further oxidized to EPTC sulfone or which reacts with GSH to yield conjugates; hydroxylation at the ethyl group to yield β-hydroxyethyl EPTC and a proposed

intermediate α-hydroxyethyl EPTC, which is cleaved to COS and CO_2; hydroxylation at the propyl group, resulting in γ-hydroxypropyl EPTC, β-hydroxypropyl EPTC and a proposed α-hydroxypropyl EPTC, which is cleaved to N-depropyl EPTC.

4.4. EXCRETION

Approximately 2-4% of ^{14}C-EPTC was excreted unchanged in the 96-hour urine of rats (Ong and Fang, 1970). Of the administered radioactivity from 2.5 mg ^{14}C-EPTC/kg ~85% was excreted as $^{14}CO_2$ by rats within 15 hours, with peak levels by 1-2 hours. As the dose level increased, a smaller percentage of radioactivity was detected as $^{14}CO_2$ and a greater percentage was found in the urinary metabolites (Ong and Fang, 1970), but no dose-related differences in CO_2 or urinary excretion patterns were noted by Hubbell and Casida (1977).

Mice expired ~40% of the administered 100 mg/kg dose of ^{14}C-EPTC as $^{14}CO_2$ within 12 hours (Casida et al., 1975). Of the radioactivity ~2% was excreted in the 48-hour feces of mice given 100 mg/kg doses of ^{14}C-EPTC by gavage, and ~4% was excreted in the 96-hour feces of rats given up to 385 ^{14}C-EPTC/kg. The excreted metabolites were discussed in Section 4.3. of this document.

5. EFFECTS

5.1. CARCINOGENICITY

Pertinent data regarding the carcinogenicity of EPTC were not found in the available literature and this chemical is not scheduled for testing by the National Toxicology Program (NTP, 1983).

5.2. MUTAGENICITY

EPTC was not mutagenic to any strain of Salmonella typhimurium studied by DeLorenzo et al. (1978), whether in the presence or absence of S-9, when 10-1500 µg/plate was incorporated into the medium. Carere et al. (1978) also found EPTC to be non-mutagenic in a spot test in Salmonella typhimurium or Streptomyces coelicolor regardless of activating systems.

A Russian study found no mutagenic effects on bone marrow cells of mice given a single oral dose $\geq$1/5 LD_{50} of EPTC (Kurinnyi, 1977). Based on these three studies, EPTC does not appear to be mutagenic.

5.3. TERATOGENICITY

The only information on the teratogenic effects of EPTC was found in the Russian literature. In an abstract of a study by Medved et al. (1970), it was reported that oral doses of 1/20 LD_{50} of EPTC administered daily throughout pregnancy to rats increased mortality of offspring when compared with controls. A dose of 1/200 LD_{50} had no effect.

5.4. OTHER REPRODUCTIVE EFFECTS

Three abstracts of studies from the Russian literature relative to the reproductive effects of EPTC were found. Voitenko and Medved (1973) reported no gonadotoxic effects in male rats given 3.6 mg EPTC/kg orally for 2 months. An oral dose of EPTC at 1/100 LD_{50} caused no changes in DNA or RNA of the gonads of sexually immature rats (Anina, 1975). Similarly, oral

doses of 16.6 mg EPTC/kg/day for 2 months to rats caused no changes in the levels of DNA, RNA, RNase activity or DNase activities in the testicles (Anina et al., 1975).

5.5. CHRONIC AND SUBCHRONIC TOXICITY

Very little information was encountered on the effects of long-term exposure to EPTC. An abstract of a Russian study by Olefir (1973) reported that administration of 1/20 LD_{50} of EPTC 5 times/week for 4.5 months to rats caused inhibition of nonspecific immunological activity and decreased resistance of treated rats to a staphylococcal infection.

As reported in an abstract of anotner Russian study (Pushchina, 1969), subchronic exposure (1/20 LD_{50} every 2 days for 34 days) to rats caused significant changes in the development of conditioned reflexes.

5.6. OTHER RELEVANT INFORMATION

The LD_{50}s for various species using various routes of exposure to EPTC were reported by Medved and Ivanova (1971) as:

oral - cat - 112.5 mg/kg
oral - mouse - 750 mg/kg
oral - rat - 1660 mg/kg
skin - rat - 3200 mg/kg

An acute dermal LD_{50} of 10,000 mg/kg for male rabbits was reported by Wiswesser (1976). Hubbell and Casida (1977) reported an i.p. LD_{50} of >500 mg/kg for mice. Exposure of HeLa cells for 30 minutes to a concentration of EPTC of 350 µg/mℓ resulted in a 39% inhibition of ^{3}H-uridine incorporation into RNA and a 96% inhibition of ^{14}C-amino acid incorporation into protein (Myhr, 1973).

Abstracts from the Russian literature report that a single oral dose of 1/20 LD_{50} of EPTC to rats caused hypotonia, bradycardia and decreased

respiration frequency (Matokhnyuk, 1972); and, Heinz body formation was induced in red blood cells following an unspecified minimum toxic dose of EPTC (Rusyaeva and Rusyaev, 1969).

6. AQUATIC TOXICITY

6.1. ACUTE

The acute lethal toxicity of EPTC to fish has been tested in several species (Table 6-1). The 96-hour LC_{50} for cutthroat trout, Salmo clarki, (~1 g bw) was 17 mg/ℓ and for lake trout, Salvelinus namaycush, was 16.2 mg/ℓ in 10°C water (Johnson and Finley, 1980). The bluegill sunfish, Lepomis macrochirus and goldfish, Carassius auratus, had 96-hour LC_{50} values of 22.6 and 25.2 mg EPTC/ℓ, respectively (Schneider, 1979). Johnson and Finley (1980) reported that water temperature (5-15°C), pH (6.5-8.5) and water hardness (44-300 mg/ℓ as $CaCO_3$) had little effect on toxicity to the trout species.

Several other parameters of acute toxicity to fish are shown in Table 6-1. The 48-hour LC_{10} of the channel catfish was reported to be near 10 mg/ℓ (McCorkle et al., 1977), while the 24- and 48-hour LC_{10} values for the white mullet were both 20 mg/ℓ (Butler, 1963a). The 24- and 48-hour EC_{50} values (effective concentration to inhibit righting response in 50% of the animals) for Fundulus similis were both 20 mg/ℓ (Butler, 1963a).

The acute toxicity of EPTC has been determined in five crustacean species, a mollusk and an aquatic worm (Table 6-2). The 24- and 48-hour EC_{50} values for loss of equilibrium in the blue crab, Callinectes sapidus, were both 20 mg/ℓ (Butler, 1963a). In white shrimp, Penaeus setiferus, EPTC at 0.63 mg/ℓ for 24 hours caused loss of equilibrium, while 48-hour exposures at this concentration caused paralysis or mortality in 50% of the organisms. The 24-hour LC_{20} in white shrimp was 1.0 mg/ℓ (Butler, 1963b). The isopad, Asellus sp., and the scud, Gammarus fasciatus, were somewhat more resistant to EPTC with 96-hour LC_{50} values of 23-66 mg/ℓ (Sanders, 1970; Johnson and Finley, 1980). The 48-hour LC_{50} and 96-hour

TABLE 6-1

Acute Lethal Effects of EPTC to Fish

Species	Duration	Concentration (mg/ℓ)	Method	Effect	Reference
Bluegill Sunfish, Lepomis macrochirus	96-hr	22.6	NR	LC_{50}	Schneider, 1979
Goldfish, Carassius auratus	24-hr	28.5	NR	LC_{50}	Schneider, 1979
	48-hr	26.8	NR	LC_{50}	Schneider, 1979
	96-hr	25.2	NR	LC_{50}	Schneider, 1979
Channel catfish, Ictalurus punctatus	48-hr	<10.0	static[a]	LC_{10}	McCorkle et al., 1977
Long-nose killifish, Fundalus similis	24-hr	20.0	NR[b]	EC_{50}[c]	Butler, 1963a
	48-hr	20.0	NR[b]	EC_{50}[c]	Butler, 1963a
White mullet, Mugil curema	24-hr	20.0	NR[d]	LC_{10}	Butler, 1963a
	48-hr	20.0	NR[d]	LC_{10}	Butler, 1963a
Weatherfish, Misgurnas fossilis	45-day	1.4	NR	LC_{50}	Perevozchenko, 1975
Cutthroat trout, Salmo clarki	96-hr	17.0	static[e]	LC_{50}	Johnson and Finley, 1980
Lake trout, Salvelinus namaycush	96-hr	16.2	static[e]	LC_{50}	Johnson and Finley, 1980

[a]Water conditions: Temperature = 20-21°C; Hardness = 22 mg/ℓ; pH = 8.2; Alkalinity = 80 mg/ℓ

[b]Water temperature = 28°C

[c]Inhibited righting response

[d]Water temperature = 19°C

[e]Water temperature = 10°C

NR = Not reported

TABLE 6-2

Acute Lethal Effects of EPTC to Other Aquatic Organisms

Species	Duration	Concentration (mg/ℓ)	Method	Effect	Reference
Blue crab, Callinectes sapidus	24-hr	20.0	NR[a]	EC_{50}[b]	Butler, 1963a
	48-hr	20.0	NR[a]	EC_{50}[b]	Butler, 1963a
White shrimp, Penaeus setiferus	24-hr	0.63	NR[c]	EC_{50}[b]	Butler, 1963b
	24-hr	1.0	NR[c]	LC_{20}	Butler, 1963b
	48-hr	0.63	NR[c]	EC_{50}[d]	Butler, 1963b
Water flea, Daphnia magna	48-hr	4.7	NR[e]	LC_{50}	Koval'chuk et al., 1971
	96-hr	9.4	NR[e]	LC_{100}	Koval'chuk et al., 1971
Isopod, Asellus sp.	96-hr	23	static	LC_{50}	Johnson and Finley, 1980
Scud, Gammarus fasciatus	24-hr	43.0	constant flow	LC_{50}	Sanders, 1970
	48-hr	35.0	constant flow	LC_{50}	Sanders, 1970
	96-hr	23.0	constant flow	LC_{50}	Sanders, 1970
	96-hr	66	static	LC_{50}	Johnson and Finley, 1980
Eastern oyster, Crassostrea virginica	96-hr	5.0	NR[f]	EC_{43}[g]	Butler, 1963a

TABLE 6-2 (cont.)

Species	Duration	Concentration (mg/ℓ)	Method	Effect	Reference
Worm, Tubifex tubifex	48-hr	18.5	NR	LC_{50}	Voronkin and Loshakov, 1973

[a]Water temperature = 20°C

[b]Inhibited righting response; loss of equilibrium

[c]Water temperature = 15°C; Salinity = 29 ppt

[d]Mortality or paralysis

[e]Water temperature = 19-22°C

[f]Water temperature = 29°C; Salinity = 24 ppt

[g]Reduction of shell growth

NR = Not reported

LC_{100} for Daphnia magna reported in a Russian abstract were 4.7 and 9.4 mg/ℓ, respectively (Koval'chuk et al., 1971). Butler (1963a) reported that 43% of the eastern oysters exposed to 5.0 mg EPTC/ℓ for 96 hours showed a reduction in shell growth. In a Russian abstract, Voronkin and Loshakov (1973) reported a 48-hour LC_{50} value of 18.5 mg EPTC/ℓ for the oligochaete worm, Tubifex tubifex.

6.2. CHRONIC

A 45-day LC_{50} value of 1.4 mg EPTC/ℓ for the weatherfish, Misgurnus fossilis, was reported in a Russian abstract (Perevozchenko, 1975). Additional data on the chronic toxicity of EPTC to aquatic organisms were not located in the available literature.

6.3. PLANT EFFECTS

The effect of EPTC on the algae, Chlamydomonas eugametos, was tested by Hess (1980). At 1.9 mg/ℓ, C. eugametos (exposed for 48 hours) showed no inhibition of growth. At 19.0 mg/ℓ for 48 hours, however, growth was decreased by 52% (Hess, 1980). Butler (1963a) reported that EPTC at 1.0 mg/ℓ for 4 hours had no effect on the growth and productivity of a "natural community" of phytoplankton. Growth, as measured by optical density, was not inhibited in Chlorella pyrenoidosa (green algae) by a 1-day exposure to 1.0 or 10.0 mg EPTC/ℓ (Kratky and Warren, 1971). Racz and Lasztity (1978) reported in an abstract (Hungarian) that EPTC at 0.019 and 0.189 mg/ℓ inhibited growth of C. vulgaris, but did not decrease chlorophyll content. The biosynthesis of complex lipids in Chlorella ellipsoidea was not affected by a 90-minute incubation with 5.0 mg EPTC/ℓ (Sumida and Ueda, 1973). The growth of Dunaliella bioculata, a unicellular marine algae, was inhibited by 0.028-0.057 mg EPTC/ℓ depending on light conditions (Grizeau et al., 1982).

6.4. RESIDUE

Pertinent data regarding EPTC residues in aquatic organisms were not located in the available literature. However, a very low BCF of 12-22 has been predicted (Kenaga, 1980).

6.5. OTHER RELEVANT INFORMATION

Olson and Christensen (1980) reported that EPTC at 4.0×10^{-3}M (756 mg/L) reduced the activity by 50% of muscle acetylcholinesterase isolated from fathead minnows, Pimephales promelas.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

The only information regarding guidelines for use of EPTC was found in an abstract of a Russian report. Medved and Ivanova (1971) recommended limiting workers to EPTC exposures of <135 mg/m^3 for 1.5 hours to protect them from skin irritations.

7.2. AQUATIC

Guidelines and standards for the protection of aquatic organisms from the toxic effects of EPTC were not found in the available literature.

8. RISK ASSESSMENT

As discussed in Sections 5.2. and 5.3. of this document, no carcinogenicity studies of EPTC were available in the published literature, and EPTC does not appear to be mutagenic based upon three studies (DeLorenzo et al., 1978; Carere et al., 1978; Kurinnyi, 1977).

Reports from the Russian literature by Olefir (1973), Pushchina (1969) and Medved et al. (1970) indicate that repeated doses of 1/20 LD_{50} of EPTC have adverse effects on rats. Medved and Ivanova (1971) defined the oral LD_{50} of EPTC to rats as 1660 mg/kg; 1/20 of this value is 83 mg/kg.

Rats receiving 83 mg EPTC/kg 5 times/week for 4.5 months were less resistant to infection than were untreated rats (Olefir, 1973). Subchronic exposure to 83 mg EPTC/kg every 2 days for 34 days caused significant changes in the development of conditioned reflexes (Pushchina, 1969). Medved et al. (1970) observed increased mortality of offspring from rats receiving daily oral doses of 83 mg EPTC/kg throughout pregnancy. Doses of 0.83 mg/kg had no effect.

Although it appears from these Russian studies that doses of 83 mg EPTC/kg have adverse effects on rats and that 0.83 mg/kg may be a NOEL, the information from the abstracts is not adequate for deriving a value for an ADI.

Statements concerning available literature in this document refer to published, quotable sources and are in no way meant to imply that confidential data, which this document could not address, are not in existence. These data, which are considered Confidential Business Information (CBI), are available in summary form as a CBI Appendix that can be accessed by individuals with appropriate clearance. Conclusions from the CBI Appendix regarding risk assessment can, however, be presented in this chapter.

The CBI Appendix to this document reviews other animal data from which an ADI of 0.05 mg/kg bw/day or 3.5 mg/day for a 70 kg man was derived. The ADI was based on a NOAEL of 5 mg/kg bw/day for prolonged clotting factor times in rats in a 1-year feeding study and an uncertainty factor of 100 (10 to account for interspecies extrapolation and 10 for protection of unusually sensitive individuals within the population).

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APPENDIX: LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of:

CA SEARCH (Files 308, 309, 310, 311, 320)
TOXLINE
MEDLINE
RTECS
SCI SEARCH
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
EPCASR
Chemical Industry Notes

Most of these searches were conducted in February, 1983; a few were conducted March-May, 1983. In additional, hand searches were made of Chemical Abstracts (Collective Indices 7 and 8th), and the following secondary sources were reviewed:

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